Darwinian natural selection: its enduring explanatory power

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Evolutionary theory has never had a stronger scientific foundation than it does today. In a short review I hope to portray the deep commitment of today's biologists to Darwinian natural selection and to discoveries made since Darwin's time. In spite of the scientific advances in the century and a half since the publication of *On the Origin of Species*, Darwin still remains the principal author of modern evolutionary theory. He is one of the greatest contributors of all time to our understanding of nature.

> An awesome gulf divides the pre-Darwinian world from ours. Awesome is not too strong a word. . . . The theory of natural selection revolutionised our understanding of living things, furnishing us with a comprehension of our existence where previously science had stood silent. –Helena Cronin (1)

The deluge continued day after day on the tiny island of Daphne Major in the Galápagos Islands, 600 miles off the coast of Ecuador. Dusty soil from years of drought washed in torrents down the steep volcanic slopes into the surrounding sea. Plants began to sprout that had lain dormant for years, and vines grew up the tent poles of the researchers on the only flat ground high up near the extinct volcano's rim. Some plants producing large seeds were smothered by the prolific vines, and others flourished. The finches on the island celebrated by "going crazy," in the words of one researcher—the males sang, established territory, and mated. The young grew fast on the insects that appeared all over the island, and they began mating at an unusually young age. The findings from this unusual year provided stunning evidence that natural selection was working on *every generation* of ground finches, changing the calculus of reproductive success and the composition of alleles in the gene pool of the species.

The biologists Peter and Rosemary Grant began studying Darwin's finches in 1973, and their research has continued full-time ever since (2, 3). It is the longest field study in biology other than that of Jane Goodall, who has studied chimpanzees in Tanzania since 1962. Younger biologists have assisted the Grants in their study, so that the ground finches of Daphne Major have been studied in great detail every year since 1973.

Daphne Major is a volcanic cone with a central crater; the island is only one half mile long *(Figure 1)*. No tourists visit the island because there is no place to land. Steep cliffs encircle almost the entire perimeter, some with reverse slopes and all with waves battering their sides. Embarkation onto the slopes involves maneuvering a small boat next to an area of relatively flat volcanic surface and jumping onto the surface as the wave hovers briefly at the right level. For researchers, this means negotiating the hair-raising landing while carrying tents, food, and research equipment.

This inaccessibility has made the island an ideal place for the isolated study of animals that have arrived by water or by air and have established a foothold and reproduced. Island species are free from the competition of innumerable mainland species, but are faced with the challenge of how to exploit the sparse resources of their small world.

Ground finches on the island are tame, letting researchers walk up to them at times and even landing on their arms as they are measuring the beak size of one bird with calipers. Because they don't migrate, they are available for study year

Figure 1. An extinct volcanic cone forms the tiny island of Daphne Major in the Galápagos, home of one of the longest studies of natural selection acting on single generations in the wild. Reprinted with permission from Grant PR, Grant BR. *How and Why Species Multiply: The Radiation of Darwin's Finches.* Princeton, NJ: Princeton University Press, 2008.

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round. There is no obstructing vegetation to hamper observations with binoculars. There are no tourists to disturb the fiches or the researchers. For these reasons and more, the island has been described as a natural laboratory.

In 2008 the Grants, who teach biology at Princeton, published a scientific volume about their study. Their findings would have been stunning to Charles Darwin, who believed that evolutionary changes brought about by natural selection would become evident only after long periods of time. Instead, *every generation* of ground finches has produced evidence of changes in morphology and allele frequencies in the population of one ground finch, *Geospiza fortis*. The birds and their genes were changed by the severe selection pressures of the years of harsh drought; small seeds were scarce, and those individuals with smaller beak depth and smaller body size died. Evolution placed a meaning on *death*. Through the death of individuals less fit in the prevailing environment, alleles coding for less useful variations became less common in the gene pool. This is nothing less than evolution occurring in real time, measurable in only months, and brought about only by natural selection—the differential survival of alleles that code for more useful traits.

The beak of finches is their secret for manipulating seeds. In his superb book about the Grants' research, *The Beak of the Finch*, Jonathan Weiner reminded us (4): "Beaks are to birds what hands are to us. They are the birds' chief tools for handling, managing, and manipulating the things of this world. . . . Each beak is a hand with a single permanent gesture." Beaks are continually reshaped to maximize their efficiency in crushing seeds of specific sizes and shapes and can be compared to pliers and wrenches *(Figure 2).*

Torrential rains came to the Galápagos in 1983 during the most severe El Niño event in 400 years, as documented in the coral reef fossil record. Research data from this 1 year on Daphne Major required still another year for entering it all into a computer. The final analysis was stunning: birds with large bodies and deeper beaks were dying; small birds with less deep beaks were thriving. Natural selection had *reversed its direction*. Now on the island small seeds were abundant, and trees producing large seeds were choked by vines. Death of the less fit became an evolutionary "force," and the gene pool of *G. fortis* changed again. So did the morphology of the birds, which were now smaller in average body size, with a more pointed beak than in the 1970s. Generation by generation, natural selection could be monitored as it occurred.

These findings are robustly documented by elaborate analyses involving 1) beak and body measurements of thousands of birds on the island, 2) observations of behavior, 3) studies of embryonic development, and 4) genetic sequencing of both nuclear and mitochondrial DNA. The issue of fundamental complexity is thus addressed: morphology, behavior, and the genetic code itself changed *pari passu* with selection pressures. One may argue that this is only correlation, but it is such consistent and remarkable correlation that causation is the only reasonable conclusion. There is no contender for causation other than natural selection. Over the years since these early studies,

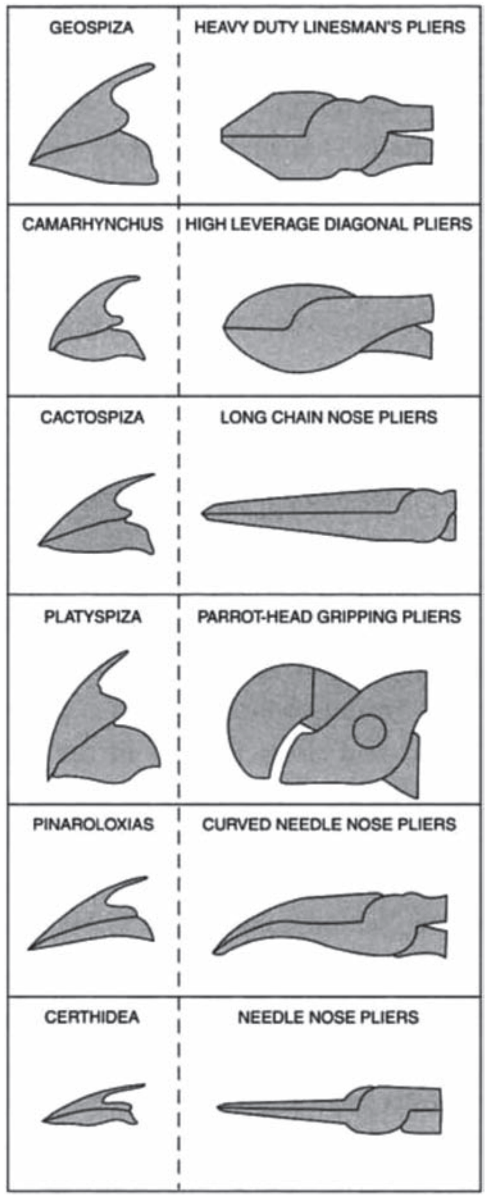

Figure 2. Bird beaks are like pliers and wrenches, each adapted to its own narrow task, and are constrained in their size and shape by the demands of the ongoing environment in which the bird lives and reproduces. Reprinted with permission from Grant PR, Grant BR. *How and Why Species Multiply: The Radiation of Darwin's Finches.* Princeton, NJ: Princeton University Press, 2008.

findings have enabled testing through predictions, in which the correlation has remained true.

Natural selection is no more, no less, than the changing representation of alleles that code for traits selected for by the environment. It is not a "force," although "evolutionary force" is an expression that is often used to describe it. It is just the differential survival of alleles in succeeding populations. The environment may be natural or artificial; we know that our artificial environment of antibiotics provides a selective force for alleles in microorganisms that contribute to antimicrobial resistance. There is no fundamental difference in the dynamics of natural and artificial selection. Darwin knew this and began his major opus with a long discussion of the domestication of animals and plants as an excellent analogy to natural selection in the wild.

The term "islands" refers not only to oceanic islands, but also to freshwater lakes separated from each other (in which innumerable fish species have evolved, for example, the African cichlids), and even to human bodies, in each of which HIV-1 evolves into a smorgasbord of "quasispecies" variants over the course of infection. The field of biological science that addresses geographic diversity is called *biogeography*. Geographic isolation enables a population to evolve without the intermixing of genes from other populations. Sometimes that proceeds to speciation, or the creation of a new species—reproductively isolated from other species. At other times it may go part of the way, with the creation of variants or subspecies.

When I recently visited the White Sands National Monument in Arizona, I learned of a striking example of natural selection on the "islands" of extremely white sand dunes, which are made of gypsum (hydrated calcium sulfate) sand crystals. The dunes are so white that they resemble a snowscape. Three small diurnal (day-active) lizards live in the dunes, having recently evolved from closely related species that live in the brown soils of the surrounding Chihuahuan Desert. The White Sands species are no longer brown but almost white, perfectly mimicking the color of the sands *(Figure 3).* When mating, they demonstrate a preference for white color morphs if given a choice in laboratory tests. Researcher Erica B. Rosenblum of the University of California at Berkeley has found a genetic basis for this color change, stemming from mutations in the melanocortin-1 receptor gene, which has a key role in producing melanin in vertebrates (5). She explained to me that the change is caused by allelic variants conferring adaptive coloration, not by epigenetic gene silencing or by phenotypic plasticity (variable phenotypic expression without genetic change). It thus represents true genetic differentiation brought about by natural selection operating in a relatively new environment. The fast-track evolution reminded me of the Galápagos finch study; in fact, the White Sands newspaper sported the headline, "The Galápagos Islands of North America!"

Figure 3. The bleached earless lizard, which lives only in White Sands National Monument, New Mexico, has evolved in only 2000 to 6000 years from a darker form living in the surrounding sands of the Chihuahuan Desert. The color change, along with changes in several other traits, has been mapped to gene mutations favored by natural selection. Photograph by Greg and Mary Beth Dimijian.

Natural selection is one of the pillars of contemporary evolutionary theory. Nevertheless, there are other causes of biotic evolution, some of which were unknown to Darwin. These are addressed after a further elaboration on natural selection.

MORE ABOUT NATURAL SELECTION

Bricolage is a wonderful French word, the best English translation being "tinkering." It was first used by François Jacob in 1977 to describe how evolution uses "whatever he [a tinkerer] finds around him whether it be pieces of string, fragments of wood, or old cardboards" to fashion new structures or behavior coded for by genes. Jacob explained: "Evolution does not produce novelties from scratch. It works on what already exists. . . . The appearance of new molecular structures during much of biological evolution must, therefore, have rested on alteration of preexisting ones" (6).

Biological structures are thus *palimpsests*, with layers upon layers of history, like an old scroll erased and written over many times. One example is the vertebral column, which has been tinkered with and modified many times in vertebrate history. In the evolutionary history of whales, there is a stunning discovery: the pelvis becomes detached from the spine, as it is no longer needed to support hind limbs. The whale's range of spinal motion is thus increased, and tiny hind limbs appear in the soft-tissue areas of fossils as relics of ancestors, destined to disappear completely in modern whales.

Other structures in animals are rendered obsolete, such as eyes in some cave-dwelling fishes. The term *vestigial* has been used to describe these structures; they are remnants of organs once useful to an evolutionary ancestor. Genes are no exception; innumerable examples of vestigial genes, some "rusting away" like submarines on the ocean floor, have been uncovered in animal genomes.

For bird lovers, a striking example of *bricolage* and co-opting of earlier structures is the avian feather. In the past decade paleontologists have found hundreds of fossils of feathered dinosaurs, some with fluffy down, some with simple barbs, still others with hollow filaments. The transition from scales to feathers may have hinged on a relatively simple genetic switch. What adaptive benefits might feathers have conferred on dinosaurs? *The same that they confer on birds today:* warmth, cryptic coloration, showy patterns used in courtship, and possibly gliding to the ground from low platforms. One chicken-sized dinosaur had feathers on arms, legs, and toes. Even though these feathered dinosaurs were not capable of flight, protofeathers and true feathers may have paved the way for true flight millions of years later. It's an example of "exaptation," the assignment of a new adaptive function to a structure that evolved under different selective pressures in an earlier environment.

The evolution of vertebrate limbs from the fins of fish is yet another example of a new assignment (by natural selection) to an earlier structure. Fossil finds have recently come one after the other. *Tiktaalik*, a 375-million-year-old fossil found in 2004, is the colorful name given to a fish skeleton with gills, the first neck, and the first front limbs; the limbs consisted of a functional wrist, elbow, and shoulder—the owner could "do push-ups." More recently, in 2011, came the discovery of pelvic-fin muscles in the first fishes to emerge on land (7). Here was evidence of a weight-bearing pelvis, hindlimbs, and their associated musculature—and the "rear-wheel drive" strategy that characterizes terrestrial locomotion in most vertebrates. Play the fossil frames in a movie sequence and you see the emergence of fishes onto land.

Even the abrupt Cambrian "explosion" of life 541 million years ago is yielding up its secrets. There is growing evidence from molecular sequences, molecular clocks, and developmental histories that most of the Cambrian fauna originated tens to hundreds of millions of years before the onset of the Cambrian, leaving a clear fossil signature only in the Cambrian (8). Darwin has been vindicated in his prediction that this apparent anomaly would some day be resolved with evidence of ancestral lineages leading up to the explosive appearance of fossils in the Cambrian.

Paleontologists stress that it is time to move past the simplistic question, "Where are the missing links in the fossil record of life?" Instead, it is time to accept that 1) the fossil record is now extraordinarily rich, and 2) a seamless record is an impossible goal. Any transition between fossils will always be a "missing link."

If you think the above examples of *bricolage* are amazing, get ready for this one. The stapes (or stirrup, the innermost of the three middle-ear bones) originated as the hyomandibular bone in fishes, supporting the gills. It later migrated to the hard palate, which it braced against the cranium in jawed fishes and the earliest tetrapods. It made a third change to become the columella in the middle ear of birds and the stapes of the middle-ear bones in mammals. *Now a hearing aid, it was once a feeding aid and even earlier a breathing aid.* And there is this: When an immature opossum is born, it climbs into its mother's pouch with its future ear bones still articulating its jaws. The stapes will migrate to the middle ear as the embryo develops. There is hard anatomical evidence supporting these anatomical transitions (9). What better example is there of a "fossil record" in development?

Remember that for natural selection to act, there must be 1) genetic variation in a population, 2) occasional mutations, and 3) mixing of genetic entities, either during reproduction (as in eukaryotic sexual reproduction) or in horizontal gene flow (as in bacteria and viruses).

Crypsis (hiddenness) is a relatively simple case of natural selection. It refers to camouflaged body color or shape, and to behavior that enhances concealment. We have discussed crypsis in lizards in the White Sands National Monument. *Behavioral crypsis* is obvious in the immobility and squinted eyes of the Scops Owl on the bare tree branch in the Okavango Delta of Botswana *(Figure 4).* It is useful for hiding from predators (if you are potential prey) or for remaining unseen by potential prey (if you are a predator). The role of natural selection is inferential, but no other explanation comes close. Alleles arising by chance mutations, which cause crypsis, render an animal less visible to predators or prey. Such alleles are more successful than competitor alleles in getting into the next generation, by virtue of the benefits they confer. The mutations may be random, but natural selection is anything *but* random.

Figure 4. Only 8 inches tall, the Scops Owl is almost invisible on the bare branch that is its home, in the Okavango Delta of Botswana. Its extraordinary camouflage includes anatomy and behavior: its breast feathers resemble tree bark, and it remains immobile during the day, keeping its eyes closed so that it is less likely to be spotted by Africa's diurnal birds of prey. Photograph by Greg and Mary Beth Dimijian.

Mimicry is another relatively simple example of natural selection. If one animal is toxic to predators, and predators learn to avoid it, another animal will benefit from mimicking the same disguise. A hawkmoth caterpillar in a Costa Rican cloud forest displays conspicuous eyespots (its real eyes are tiny) and a soft, fake stinger *(Figure 5).*

Do *plants* ever "lie"? Consider the passionfruit vine, often parasitized by butterfly eggs that hatch into caterpillars. The caterpillars feed on the leaves. If mutations occur in the plant that produce light-colored spots on the leaves *(Figure 6),* they might just resemble eggs laid by *Heliconius* butterflies. Experiments have shown that these butterflies are less likely to lay eggs on host plants that have eggs or egglike plant structures (10). Again, natural selection is the only candidate explanation.

What about bacteria and viruses? Even though they don't reproduce sexually, they both enjoy high levels of horizontal gene transfer ("parasexual reproduction") and maintain populations with high genetic diversity. There is thus ample variation for selection to act on. Under an antibiotic regime, selection occurs exactly as in Darwin's finches on the Galápagos. Differential death is the great reaper, eliminating the less fit.

Figure 5. Munching on a plant stem in Costa Rica's Monteverde Cloud Forest Reserve, this Xylophanes caterpillar exhibits fake eyes and stinger. Its real eyes are so tiny that you would need a hand lens to see them. Photograph by Greg and Mary Beth Dimijian.

Figure 6. Do plants tell lies? Passionflower vine leaves in Costa Rica do, preserving mutations that produce spots closely mimicking eggs of *Heliconius* butterflies. Plants with the spots are protected from caterpillar predation because butterflies choose to lay their eggs on other plants. Photograph by Greg and Mary Beth Dimijian.

Antibiotic resistance occurs not only in modern medicine but also in nature, where microbes, plants, fungi, and insects make their own antimicrobials. It is no surprise to find that these natural antimicrobials must keep evolving in the universal host-pathogen arms race. A study in 2011 demonstrated antibiotic resistance genes comprising part of fossil bacterial DNA 30,000 years old. Those same genes are found today in modern bacteria, where they encode resistance to beta-lactam, tetracycline, and glycopeptide antibiotics (11).

Just think: before Darwin, *essentialism* was the prevalent view of nature. Each species had an "essence" that was as unchanging as chemical elements in the periodic table. Each plant and animal species was believed to have originated in the same form as we see it today.

DOMESTICATION OF ANIMALS

> Domestication is not just an excellent analogy of natural selection. It's also a good experiment. –Richard Dawkins (12)

The best experiment ever made in animal domestication (13, 14) is the ongoing study of silver foxes, initiated in the 1950s by the Russian geneticist Dmitry K. Belyaev *(Figure 7)*. On a Siberian fur farm, Belyaev raised silver foxes, *Vulpes vulpes*, and observed the young of each litter. Without prompting, he and his coworkers noted which juveniles were friendly and which avoided human contact. The friendly "tame" ones were later mated with tame members of other litters, and this mating selection was performed generation after generation. *Only tameness* was selected for. Now, over 50 years later, the result is a breed of foxes never imagined before: friendly from birth, begging for attention, and with striking anatomical changes: a piebald coat color (with a white patch on the top of the head, seen in border collies, pigs, horses, and cows), short legs, a curled-up tail, and floppy ears. Charles Darwin, who loved dogs and spent much of his life studying domestication, would have been stunned. These changes, which occurred over only 40 generations, reflect *changed timing of developmental processes*. Childlike traits prolonged into adulthood are an example of *neoteny*—neo-, "new," and -teny, "holding onto." Belyaev's unique experiment compressed into decades an ancient process that unfolded over

Figure 7. A silver fox pup shows tame and affectionate behavior, which results from selective breeding in the longest scientific study of domestication ever made, conceived by the Russian geneticist Dmitry K. Belyaev in the 1950s. Reprinted with permission from Trut LN. Early canid domestication: the farm-fox experiment. *American Scientist* 1999;87(2):160–169.

centuries. Instead of foxes, *wolves* are believed to be the ancestral canids that were domesticated into the hundreds of dog breeds that have become our "best friends" *(Figure 8).*

Dog fossils have been found at archeological sites dating from 11,500 to 15,500 years ago (15). It is not surprising that dogs were domesticated long ago. They have served humans as close companions, guard dogs, police dogs, herding dogs, hunting dogs, sled dogs, military dogs, seeing dogs for the blind, and olfactory search dogs. Have dogs domesticated us as well? They may have secured equally important services from us, from feeding to family membership. There is, however, at least one example of a serious disservice we are guilty of: the bulldog's craniofacial malformation, in which facial shortening has created severe medical problems *(Figure 9).* In the bulldog's unfortunate outcome, domestication differs from natural selection. Such a defective phenotype would quickly be eliminated from the reproductive pool by natural selection.

Figure 8. Over the past 10,000 to 15,000 years, humans have domesticated the Eurasian wolf and used its natural genetic variation to create hundreds of breeds of domestic dogs. Reprinted with permission from Ellegren H. Genomics: the dog has its day. *Nature* 2005;438(7069):745–746.

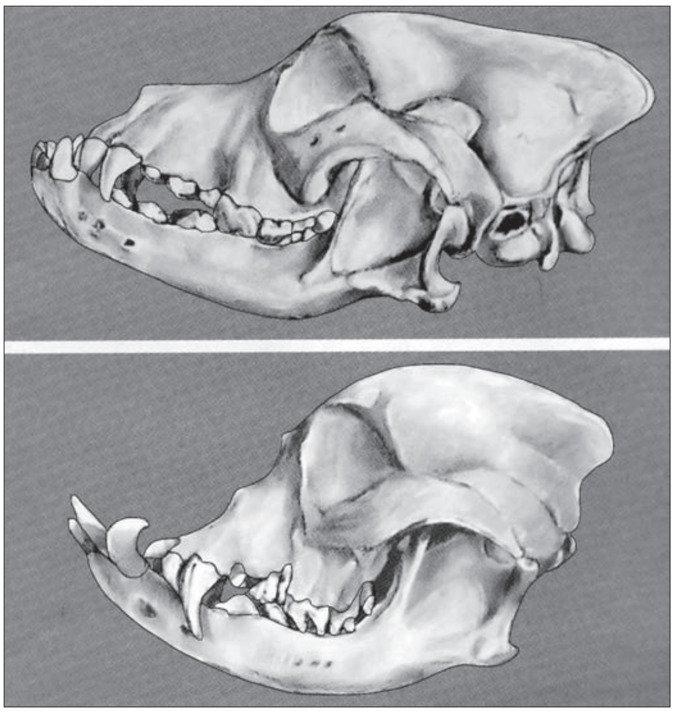

Figure 9. The bulldog skull before 1890 (top) and its unfortunate fate through selective breeding in 1935 (bottom). Craniofacial malformation has created serious medical problems, which we would attempt to correct if they occurred in humans. Reprinted with permission from Thomson KS. The fall and rise of the English Bulldog. *Amer Scientist* 1996;84:220–223.

Are we domesticating *ourselves*? Consider the following features of modern life:

- Sanitary sewerage disposal
- Clean water
- Cooking
- Refrigeration
- Clothes
- Climate control
- Modern medical care
- "Assisted reproduction"—in vitro fertilization, preimplantation genetic diagnosis, intracytoplasmic sperm injection

A more troubling question is: Are we eliminating alleles for "robust" traits from the human gene pool?

ENDOGENOUS VIRAL ELEMENTS

Viruses, especially bacteriophages ("phages," viruses that infect bacteria), may be the most numerous and ubiquitous genetic entities on the planet. Genetic sampling techniques show that seawater is a soup of viruses. Bacterial turnover on Earth occurs daily through the most common predator-prey relation known, that of phages and bacteria. Whether or not you choose to consider viruses as living entities, they are visible to natural selection, just as cellular genetic entities are.

There is an "archeological record" of past infections by viruses that inserted their genes seamlessly into our DNA (16). These genes are recognized by their sequence similarity to present-day viruses. Many have been found to be degraded, some more than others. Endogenous viral elements (EVEs) constitute a significant portion of our genome—as much as 8%. That's over 6 times more DNA than is found in all of our 20,000 protein-coding genes. They are replicated in Mendelian fashion every time a cell divides.

Most EVEs are retroviruses (which, like HIV-1, convert their RNA to DNA and insert it directly into our genome), but some are nonretroviral, such as Ebola-like and herpesvirus-like sequences. Retroviral EVEs are called ERVs (endogenous retroviruses) and HERVs (human endogenous retroviruses). The age of endogenous viruses can be estimated by molecular clock techniques, because they are confined to a host genome and therefore "frozen" in a slower mutational state than freely existing viruses.

EVEs constitute direct evidence that modern viral lineages have very ancient roots. Lentiviruses are 2 to 4 million years old; filoviruses, 12 to 30 million years. The science writer Matt Ridley has said: "If you think being descended from apes is bad for your self-esteem, then get used to the idea that you are also descended from viruses" (17).

PALEOANTHROPOLOGY

During only the past decade, fossil discoveries in Africa, Asia, and the Near East have provided an extraordinary sequence of the transition from arboreal to terrestrial locomotion in early hominins. One of the defining characteristics of hominins is bipedalism, and we are fast approaching an almost seamless fossil record of skeletal adaptations progressing through intermediate stages to fully bipedal, with the requisite changes in foot, ankle, knee, pelvis, vertebral column, upper extremities, and forward placement of the foramen magnum. These changes occurred as forests in East Africa were changing into a more open habitat, typical of the "wooded grasslands" of the East African savannah today. Bipedal locomotion enabled a huge increase in efficiency for traveling long distances in search of food and a new habitat, especially when carrying children.

The most stunning finding of paleoanthropology, however, has been this: in only 3 million years the hominin body size *doubled* and the brain *tripled* in volume to its present size, violating the usual "rules" of allometry. Typically in mammals, if body weight doubles ($\times 2^1$), brain weight increases not by 2^1 but by about $2^{3/4}$ or about 1.7 times. Instead, our intracranial volume increased 3 times, with the neocortex expanding the most. More sophisticated tools, long-distance trade, language, and the earliest art accompanied the encephalization. There can be no better evidence of natural and sexual selection, even though the evidence is "only" inferential and cannot be verified experimentally. Once the stage was set—with hands free to manipulate objects, brain structures capable of complex language, and an omnivore's gastrointestinal tract providing more efficient energy extraction from a diet of plants and animals—brain expansion progressed steadily and inexorably. Cooperation among kin and tribal members may have contributed significantly to survival of children, who—with their early birth and large brain—required a long period of upbringing.

PROCESSES OTHER THAN NATURAL SELECTION THAT CONTRIBUTE TO EVOLUTION, SOME UNKNOWN TO DARWIN

Natural selection is not the only process by which life evolves. I have listed other processes and mechanisms below in a short outline.

- *Sexual selection.* Proposed by Darwin and rejected by Alfred Russel Wallace, sexual selection is distinct from natural selection and involves mate choice (intersexual selection) and competition between members of the same sex (intrasexual selection). Even though sexual selection is "natural," it is not the same as natural selection and may even oppose natural selection, as in the case of male ornaments and bright colors that make the male more vulnerable to predation.
- *Endosymbiosis.* "Endo," or *inside*, and "symbiosis," or *living together*, refer to the incorporation of a microscopic organism such as a bacterium into a larger cell, such as the protoeukaryotic cell. Mitochondria and chloroplasts have all the identifying traits of bacteria, and they perform crucial functions today (ATP synthesis and photosynthesis, respectively). Most of their genes have migrated to the host cell nucleus and are integrated into the nuclear genome, seamlessly joined in a now obligate partnership—one of the most critical events in the history of the eukaryotic cell. Endosymbiosis is an example of *inheritance of acquired characteristics*, i.e., Lamarckism. Surprisingly, it is entirely compatible with Darwinian natural selection acting on each partner independently; as with other mutualisms, it confers benefits upon both partners.
- *Major extinctions.* Both fit and unfit have perished together in Earth's great mass extinctions, the latest of which—the "Anthropocene" (also dubbed the "Homogenocene")—has been proposed as being underway. (Who would doubt this?)
- *Genetic drift in small populations.* Without the buffering effect of large population size, accidents eliminate fit and unfit alike, and gene frequencies would thus change in the population, some at random.
- *"Accelerated evolution."* An increased mutation rate appears to have occurred in some gene regions of humans—one in neurons playing a key role in the developing cerebral cortex, and another in the *FOXP2* gene, involved in human speech. This accelerated mutation rate seems also to occur in some bacterial populations subjected to stress. Something is "tampering" with mutations, providing a surplus when they are needed for a diversity of lottery tickets. The mechanism of this acceleration is unknown, but it sounds as if it may be adaptive—and thus visible to natural selection.
- *Neutral protein polymorphisms.* Different structural forms of a protein that have little or no effect on the phenotype are invisible to natural selection in some environments.
- *Epigenetics and gene regulation.* See discussion immediately below.

EPIGENETICS

At the interface of gene and environment, epigenetics (epigenomics) addresses heritable changes in gene expression that cannot be explained by changes in DNA sequence. In eukaryotes and prokaryotes, epigenetic changes can activate, reduce, or completely disable a gene's activity. Epigenetic "marks" control access to DNA by different mechanisms, one of which is methylation of cytosine. Small *noncoding* RNAs ("noncoding" meaning not coding for proteins) are believed to be another agent of epigenetic change. The terms "epigenetic" and "epigenome" are still somewhat fluid and subject to change.

Early in the embryonic development of multicellular organisms, undifferentiated stem cells develop into the many different cells of the developing organism, through the silencing of genes. These changes, also called "epigenetic," usually last for a lifetime, so that a liver remains a liver. A cancer cell, however, may undergo epigenetic reprogramming, and "epimutations" may contribute to aging.

Some epigenetic marks change as the organism responds to environmental change, such as starvation, stress, or disease, and some of these marks may persist for several generations (and are thus called "transgenerational epigenetic inheritance"). Mapping the epigenome has become increasingly important as we realize that the genome holds only a fraction of the information needed to understand development and disease.

Genome-wide association studies are uncovering evidence of *polygenic* (many-genes) predisposition to specific diseases (20). Many of these genetic predispositions involve noncoding DNA that regulates gene expression. Many so-called "genetic" diseases may have their origin in such epigenetic changes.

Does epigenetics change our understanding of evolution? Two studies in 2011, one in the plant *Arabidopsis thaliana* (18) and the other in the nematode *Caenorhabditis elegans* (19), showed epimutations that changed the phenotype for only a few generations. The changes, though inherited, were unstable over short time periods. Such cycling is not characteristic of genomic DNA, which remains relatively stable over time.

Epigenetically silenced alleles seem to be taken *out of the selection pool* for short periods of time. This could affect evolution by natural selection on short time scales, but seems unlikely to be the basis of adaptations that are stable over long time periods.

Epigenetic silencing of genes appears to be a key defense against transposons, the "jumping genes" discovered by Barbara McClintock. Transposons may be the ultimate "selfish" elements in our genome. A stunning 50% or more of the human genome is derived from *retrotransposons*, a category of transposons that copy and amplify themselves through RNA intermediates. Retrotransposons pepper our genome, moving to future generations in egg and sperm. Many originate from viruses, and most are strongly *mutagenic,* inserting themselves inside genes or adjacent to genes. Some 70 human genetic diseases are strongly correlated with mutations caused by the "gymnastics" of these mobile genetic elements. The relevance of epigenetics became apparent when it was found that retrotransposons are heavily methylated and silenced epigenetically, possibly as a defense against their continuous onslaught (21).

In summary, epigenetics is of paramount importance in cellular differentiation, disease, and our defenses against endogenous and freely circulating viruses. But our understanding of its full importance in evolution is in its infancy.

EARLY LIFE EVOLUTION

The ponderous gap between amino acids on the one hand, and cellular organelles, cell membranes, and self-replicating macromolecules on the other, is too great for our current theories. We are very much in the dark about the origin of life.

Stanley Miller's famous experiments in the 1950s with electrical discharges, ammonia, methane, hydrogen, water vapor, and hydrogen sulfide were discounted in the 1990s, but came into favor again in 2008 when heat from hydrothermal vent ecosystems was considered. One current hypothesis states that RNA served as a hereditary template and catalyst, and that the ribosome evolved as a "machine" for building proteins, as it does today. Research suggests that a mineral in common clay may have played a role in the synthesis of RNA. Nevertheless, early life researchers are engaged in formalized guesswork.

Darwin thought that the "tree of life" had a *last universal common ancestor*, now known by the acronym *LUCA*. Today we believe that the trunk of the tree was a heterogeneous mix of genetic entities that traded genes wantonly by horizontal gene transfer. Vertical inheritance would evolve later. *Curiouser and curiouser.*

INFORMATION

When DNA was found to carry the genetic code, it was realized that *the information it bears is its only function*. This was hard for some biologists to swallow, as it didn't sound like biochemistry. No one had ever suspected that one organic molecule could code for others, eschewing a *chemical* function.

A digital code was clearly at the root of life. Whereas the English alphabet has 26 letters and the Greek 24, the DNA alphabet has 4 letters. Those letters spell out 3-letter words (codons) which tell the ribosome which amino acids to assemble into proteins. Was it significant—or a stunning historical accident—that binary computer science developed at the same time that we discovered the digital code of life?

Here is the heart, the pulsing core of complexity: the informational code that runs the engine of life, the complex calculus that changes under the steady beat of natural selection. The complexity of life is hardly irreducible—we hold it in our hands, and we are learning to manipulate it at the molecular level.

With selective death as a portal, evolution changes the information in the gene pool of a species, setting the stage for reproductive isolation and the origin of new species.

CONCLUSIONS

Across biological disciplines, natural selection has become accepted as a powerful and peerless explanatory principle. It is constantly scrutinizing the smallest differences among competing alleles and their phenotypic expression and has had ample time over Earth's history to shape the life forms we see around us and in the deep fossil record. The death of the individual has been its portal for changing the gene pool of a species. Through bricolage, or tinkering, it uses old parts and constructs new machines on the palimpsest of its canvas. Biology's informational code underlies the complex dynamics of life and has only recently yielded secrets that were undreamed of by Charles Darwin. Utterly without the knowledge we have gained since he published *On the Origin of Species* in 1859*,* Darwin gave us one of the most profound explanatory principles in the history of science.

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